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RADIOACTIVE IODINE IN THE DIAGNOSIS AND THERAPY OF CARDIOVASCULAR DISEASES

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[Following is the translation of an article entitled "Radioaktivnyy yod v diagnostike i terapii serdechno-sosudistykh zabolevaniy" (English version above) by Candidate of Medical Sciences A. F. Leshchinskiy (Odessa) in Klinicheskaya Meditsina (Clinical Medicine), Vol XXXVIII, No 5, Moscow, 1960, pages 27-33.]

The interest shown in radioactive iodine as a remedy for cardiovascular diseases is due to its possible restraining effect upon the functions of the thyroid gland, which are largely reflected in the state of the nervous system and metabolism, which in turn play an important role in changes in the cardiovascular system. Moreover, a number of characteristics of radioactive iodine preparations permit the use of the latter in determining the rate of blood circulation, the permeability of the walls of the vessels, the volume of blood, etc., which may serve for diagnostic purposes in cardiovascular pathology. Rational use of radioactive iodine in medical diagnostic practice is based on a knowledge of its pharmacological properties.

Pharmacological properties of radioactive iodine

In radioactive iodine preparations, two important properties are combined: the pharmacological characteristics of the compound and the presence of penetrating radiation (β- and γ-rays), which in the last analysis determine their action and the possibilities of their application in diagnosis. Among the many radioactive isotopes of iodine, I^{131} finds the greatest use for medical-diagnosis purposes, while I^{130} is less used; lately, I^{132} and I^{124} have begun to be utilized. Their half-lives are 8 days, 12.6 hours, 2.4 hours, and 4 days, respectively. In pharmacotherapy, radioactive iodine is used in the form of sodium or potassium salt; these preparations (weak solutions), as well as methyl iodide and serous albumin, tagged with radioactive iodine, are used in investigating hemodynamics.

Radioactive iodine is absorbed with great speed. After ingestion, it appears within a few minutes in the blood, the thyroid gland and the spinal-cord bluid (A. B. Asatryan, I. K. Zyuzin, V. G. Spesivtseva, Ye. A. Kolli, N. A. Shtegeman, M. N. Fateyeva, and others). The rate of resorption is determined both by the characteristics of the preparation and by a number of other factors. The intensity of absorption of subcutaneously introduced albumin tagged with I^{131} is 510 times less than the rate of resorption of NaI^{131} (B. D. Zabudskiy). Retardation of the absorption of radioactive iodine from the stomach is observed when food is present in it; after subcutaneous injection, it is observed when adrenalin is introduced or a tape (zhgut) is applied. The reverse is noted in case of hyperemia and the introduction of histamin (I. A. Cyvin).

The spread of the preparation through the organism of animals proceeds unevenly. In the first 10-15 minutes the thyroid gland absorbs the maximum of radioactive iodine: in the next few hours considerable quantities of it are detected in the kidneys. Some hours after the introduction of the indicator dose of I^{131} the series of organs may be arranged as follows with regard to the decline in iodine activity: kidneys, blood, skin, gonads, liver, adrenal glands, muscles, brain, (Gerts [Hurst ?] et al, Perlman et al).

The dynamics of the accumulation of radioactive iodine in the thyroid gland -- a "critical" organ in this respect -- depends upon very many factors. Absorption is restricted to a definite quantity (10-20 mg%) of iodine and hence depends upon the dose: the smaller the latter, the larger the precentage absorbed from the introduced quantity. It has been shown that the thyroid gland absorbs considerably more of the isotope introduced in the form of iodide than in the form of thyroxine (Joliot and others). Stimulation of the activity of the central nervous system is usually accompanied by an increase in the iodine concentration in the thyroid gland (Ye. A. Kolli, E. D. Tykochinskaya). In sleep, a diminution in the rate of iodine concertration by 1 1/2 - 2 1/2 time is detected (N. M. Draznin). Accumulation of radioactive iodine in the gland is weakened sharply by experimental neuroses (V. I. Arkhipenko) and is strengthened in case of chronic irritation of the peripheral nerves (V. V. Mamina). Hypophysectomy is accompanied by a lowering of the absorption of the isotope by the thyroid gland (G. V. Mitayev and I. A. Isachenko, Taurog and Chaikoff, and others); increase in absorption occurs when thyreotropic hormone is introduced (Gerts et al, B. V. Aleshin and N. S. Demidenko, and Peshis et al report on the influence of the sex glands on this process. In pregnancy (second half) in healthy women the accumulation of I^{131} in the thyroid gland is reduced (L. I. Lobanovskaya and Ye. M. Besedina). Suppression of the accumulation of the isotope is noted under the influence of adrenalin.

The accumulation of radioactive iodine in the thyroid gland is reduced by large doses of antithyroid drugs, cortisone and hexone, when there is a vitamin B_1 or albumin deficiency or an excess of butter in the food (N. V. Verzhikovskaya, L. A. Kashchenko; S. V. Maksimov and I. N. Sharkevich, and others). Greer and Astwood have established that vegetables have a more pronounced antithyroid action than animal products; among the products of animal origin, cow's milk, liver and oysters stand out in this respect. It should be borne in mind that in middle-aged persons the rate of accumulation of radioactive iodine is twice as great as in elderly persons, and is 1.4--1.5 times greater in women than in men (Perlmutter and Riggs). Of no less significance is the possibility of the passage of iodine through the placenta to the fetus, whose thyroid gland begins to absorb iodine at the age of two months. (Chapman and Evans).

Secretion of the larger part of the isotope occurs with the urine; only about 15% of it is carried out with the feces, sweat, expired air, saliva or milk. During the first two days 53 - 58% of the quantity introduced is secreted with the urine; during the next three days, 12-15% (M. A. Kipelovich and N. M. Draznin). Loading with iodine and employment of caffeine promote its secretion (Max and Tochinskiy, E. D. Tykochinskaya). According to Joliot, 50 times less iodide tagged with radioactive iodine than thyroxine is secreted with bile.

The information given above on the pharmacological properties of radioactive iodine determine a number of the conditions of its rational utilization. Depending upon the object pursued, the latter should insure a maximum accumulation of the isotope in the thyroid gland (curative application) or create the premises for the proper judgment of the results of the diagnostic use of the isotope. In both cases there should be a discontinuance of the introduction of the stable isotope of iodine into the organism as a medicament or as a component of roentgen contrast substances, as well as preparations of thyroid gland and antithyroid drugs. Treatment with bromides and large doses of caffeine must be interrupted. It is recommended that the ingestion of iodine-containing food be limited. This includes iodized salt, marine plants and animals (cabbage, pears, raw carrots, etc.), possessing antithyroid action. In medical practice for the purpose of heightening the accumulation of radioactive iodine in the thyroid gland, N. V. Romashkan proposes repeated (more than 1-2 times) blood transfusions of 200 ml each; there have been attempts to use thyreotropic hormone from the hypophysis for this purpose.

Very important are the questions of radioactive iodine dosage. There exist two dosing principles in its medicinal application; fractional or instantaneous introduction of the entire quantity of isotope. The former method is preferable, since in this case, with similar results from both methods, one can avoid complications and

gauge the size of the total dose and the internals between administrations by the reaction to the individual introductions. It must be borne in mind that the fractional method is used more often when there is no need for prompt surgery. As regards the dosage in the diagnostic application of radioactive iodine, minimal activities are in this case introduced into the organism, permitting determination of the necessary indices by the existing methods.

Radioactive iodine preparations are introduced on an empty stomach or into the vascular channel.

In concluding our description of the pharmacological characteristics of radioactive iodine, we consider it necessary to mention the changes in them in the presence of disorders in the nervous system or the gastro-intestinal tract, of hemodynamic changes or of the disturbance of urine secretion. This especially concerns those suffering from diseases of the cardiovascular system. Allowance for a maximum number of these factors in applying radioactive iodine will promote the best effect.

Radioactive iodine in the diagnosis of cardiovascular diseases

For diagnostic purposes, radioactive iodine may be employed in the following main directions: a) in investigating the blood circulation in the cavities of the heart and in the peripheral vessels; b) in determining the minute volume of the heart and the mass of blood; c) to establish the function of the thyroid gland in cardiovascular diseases from the absorption of the isotope.

The method of investigating the blood circulation in the heart cavities was first described (Prinzmetal and co-authors) in 1949 under the name of radiocardiography. The principle of the method is that, owing to the considerable penetrating power of the γ-radiation of the radioactive isotope, the latter, upon injection into the elbow vein, could be traced with a counter on the chest in its course with the blood stream through the heart and lungs. For radiocardiographic purposes, radioactive sodium was at first employed, but radioactive iodine was found to be more suitable. In radiocardiography, it is recommended (Beierwaltes and co-authors) that the patient in a reclining position be given with great speed 4 microcuries of I^{131} in a volume of 0.2-0.4 ml; then his arm is raised vertically so that the isotope will enter the right auricle with the blood stream. The scintillation counter is placed in the center of the contours of the heart previously drawn on the skin in the reclining position with the aid of a fluoroscope.

The graphic representation of the data obtained (rediocardiogram) from healthy persons consists in an initial high wave (R) of increased radioactivity, reflecting the moment of entry of the blood into, and exit from, the right part of the heart; and in a second, lower wave (L), reflecting the passage of the blood through the left; the descending part of the curve (T) between the

first two indicated the stay of the isotope in the lungs.

In the survey given by M. N. Fateyeva of the reports to the Second International Conference on the Peaceful Uses of Atomic Energy (Geneva, 1958), we find investigations aimed at perfecting the method of radiocardiography. There is a proposal (Monasterio and Donato) for the combined use of the albumin of human serum and methyl iodide tagged with radioactive iodine and of radioactive gold. With the aid of tagged methyl iodide introduced by inhalation, it is possible to investigate (Zheymet and Tomlinson) the characteristics of the flow of blood in the left half of the heart and myocardium. Normally, after inhalation of methyl iodide the maximum activity over the heart is recorded after 5 seconds with a rapid diminution in the course of 10 seconds, whereas in heart diseases the curve of the drop in activity is slow and drawn out.

Analysis of the radiocardiograms permits one to refine the diagnosis and make a differential diagnostic of heart diseases. According to Shipley and co-authors, the interval between the two peaks reflecting the time of circulation in the lungs and averaging 5.8 seconds in healthy persons, increases to 12.3 seconds in persons suffering from heart failure. As a result of the weakening of the systoles, the time of passage of the isotope through the heart is increased; in case of thyreotoxicosis the time of circulation is shortened. In dilatation of the left part of the heart(failure of the aortal valves or hypertension), the L wave becomes broader, while the R wave remains normal. On the other hand, in exclusively right-side dilatation, when the passage of the blood into the left half of the heart is slowed up, both waves (L and R) are broadened and overlap to some extent. To a definite extent, it is possible to differentiate the hypertrophy of the ventricles from dilatation in the radiocardiogram, since the changes described are usually not observed in muscular hypertrophy.

Uncomplicated emphysema (absence of changes in the radiocardiogram) are similarly differentiated from enphysema accompanied by a pulmonary heart (? legochnym serdtsem) with dilatation of the right part of the heart, when the R wave is reduced. The radiocardiogram may also serve to detect congenital defects of the heart. Thus, in Fallow teratology the L wave is absent or poorly pronounced, whereas the R wave remains normal. In the presence of ductus arteriosus in the radiocardiogram the L wave and a part of the T curve are not expressed; operation leads to normalization of the radiocardiogram.

By using various places for the introduction of radioactive iodine, one can determine stoppage of the upper vena cava from the radiocardiogram. In this case, upon injection of the isotope into the femoral vein, a rapid rise in the R wave is observed, whereas this wave appears and rises slowly when it is introduced into the elbow vein.

In studying the circulation in the peripheral vessels with the aid of radioactive isotopes on the basis of the determination of their disappearance from the vascular channel after introduction, serous albumin tagged with radioactive iodine is used instead of the radioactive sodium, the advantage of the former being the lack of the power, peculiar to an electrolyte, to diffuse through the walls of the capillaries, which considerably affects the indices of the state of the circulation. The method consists in that, with a constant room temperature after placing the scintillation counter in the area of the foot or wrist, the radioactivity of the albumin tagged with I^{131} and introduced into the elbow vein (75-100 microcuries in less than 1.5 ml of solution) is recorded for a long time. Three sections are distinguished in the curve of activity: 1) a short period of absence or small rise of activity - - the time taken by the isotope to spread from arm to leg; 2) growth of activity --- recording the rate of mixture of the isotope with the blood; 3) the plateau part of the curve, indicating complete mixing of the albumin with the blood. Of the greatest significance is the inclination of the second half of the curve, since it is mainly governed by the quantity and rate of flow of the blood in the field under the counter, i.e. by the clearing of the isotope from the capillary channel. Reduced resistence of the peripheral vessels results in an increased inclination of the curve; the reverse is observed when the resistence of the vessels rises. In clinical practice, this method permits one to solve the question of whether the manifested affection of the skin (ischemic necrosis) of the extremity is the result of a reduction in blood supply; it can aid in establishing a diagnosis of obliterating endarteriitis. The method is of significance in the evaluation of vascular reaction, and in the determination of the results of treatment (Macintyre and co-authors). The application of radioactive iodine by the above-described method permits one to calculate, first, the minute volume of the heart in liters per minute

$$\frac{\text{Total introduced activity} \times 60}{\text{Sum of activities determined each second}} \times 100;$$

and, secondly, the average time of curculation $\frac{\Sigma(C \cdot t)}{\Sigma C}$,

where C is the activity per second, and t the interval in seconds from the beginning of the curve to the period when the concentration was recorded; thirdly, the volume of blood in the lungs:

$$\frac{\text{Minute volume of the heart (ml/min)}}{60} \times \text{average time of circulation.}$$

Radioactive iodine in the form of NaI^{131} or tagged albumin is used (Zankel and co-authors) to determine the time of curculation in the vena safena --- the period of the spread of the isotope from the place of injection (rear medial vein of the foot) to the area of the junction of the vena safena with the vena femoralis. In case of thrombosis of a vein or artery, the blood stream is slowed

down, being normally about 47 seconds.

The indices of the volume of blood, which have a certain clinical significance, can also be determined with the aid of albumin tagged with I^{131} (Storaasli and co-authors). For greater accuracy, the blood volume is also investigated simultaneously with the aid of azo dyes. The principle of the method consists in the calculation of the total mass of blood and the volume of plasma by the degree of dilution of the iodine albumin introduced. A certain volume (20 ml) of radio-iodine albumin with a definite activity (12 microcuries) is introduced intravenously; after 10 minutes a blood sample is taken from the vein of the other arm and the activity in it is determined (separately in the plasma) after centrifugalization. Knowing the activity and the hematocrite, one can calculate the volume of the blood. In the interpretation of the data obtained, there are certain difficulties in establishing the limits of the individual values of the volume of blood and plasma. Crispel and co-authors have fixed the total volume of blood at 82.3 ml/kg, the volume of plasma at 48.9 ml/kg, noting a gradual diminution of these indices with increase in age. Sklyarov has also established considerably lowered indices in 89 (53 women and 36 men) healthy old persons (60--99 years). Thus, the blood volume averaged 55.4 ml/kg for men, and the plasma volume 31.6 ml/kg; for women, 60.7 and 36ml/kg, respectively. The author points out the great significance of the determination of these indices in elderly persons before surgical operations, the outcome of which depends to a considerable extent upon the volume of blood.

According to data from a number of researchers, an increase in blood volume is observed in true polycytemia, excessive compensation after loss of blood, congestive heart failure, cirrhosis of the liver, thyreotoxicosis, non-coalescence of the septum between the left and right parts of the heart, etc.; in cases of heavy bleeding, shock, burns, myxedema, etc., a diminution of the volume of circulating blood is noted. Among the diseases cited there are also some that are accompanied by changes in the cardiovascular system.

Investigation of the absorption of radioactive iodine by the thyroid gland in cardiovascular diseases pursues the object, firstly, of establishing the functional state of the gland, especially in disorders of respiration and the metabolic processes, which does not permit the use of basic metabolism as an index; secondly, of determining the possibility of the curative application of the isotope and its dosage.

M. N. Fateyeva established on the basis of 205 patients that in the first stage of hypertension absorption of I^{131} by the thyroid gland in half the patients is at the upper limits of the norm or exceeds it; in the second stage there is a tendency toward a lowering,

while in the third stage (sclerotic) in the absolute majority of cases the accumulation of iodine is lower than the normal values. Similar results have been obtained by K. L. Georgadze, V. M. Karatygin and co-authors, V. G. Spesivtseva and N. A. Terent'yeva. The lowering of the absorption of I^{131} by the thyroid gland detected by M. N. Fateyeva and K. G. Nikulin in atherosclerosis may be an additional test in the establishment of a diagnosis along with electrocardiography and the determination of the cholesterol metabolism. This method acquires significance (N. I. Chernyshova) in the differential diagnostic of atherosclerosis of the coronary vessels (repression of the inclusion of I^{131}) and functional stenocardia (normal or heightened accumulation of I^{131}).

In defects of the heart accompanied by various degrees of cardiovascular failure, some authors note a rise in the accumulation of the isotope in the thyroid gland (L. N. Kazakova, O. D. Andreyeva, Freedberg and co-authors); others note a drop (M. N. Fateyeva, A. G. Samaradashvili, V. N. Filinov, Keating et al, and others). V. G. Spesivtseva proposes the use of radioactive iodine for the differential diagnosis of concomitant hyperthyreosis in patients suffering from heart trouble.

Blumgart and co-authors have established the initial therapeutic dose of the preparation according to the accumulation of I^{131} in the thyroid gland of patients suffering from diseases of the cardiovascular system, which they then treated with radioactive iodine.

Radioactive iodine in the therapy of cardiovascular diseases

In the origin of disorders in the action of the cardiovascular system in thyreotoxicosis cases, great significance is attached to a heightening of the function of the sympathetic section of the vegetative nervous system and to the accumulation of the products of intensified metabolism, which lower the tonus of the muscles of the peripheral vessels. It is natural that therapy of thyreotoxicosis patients by radioactive iodine, accompanied by changes in the functions of the thyroid gland, the nervous system, metabolism, etc., results also in normalizing the hemodynamic indices even in the presence of nictating arrythmia, paroxysmal tachycardia or stenocardia (V. M. Karatygin et al, Z. I. Rozhnova and K. P. Kalinina, Maloof and Chapman, Beierwaltes et al, and others). However, radioactive iodine can be used in therapy of patients suffering from cardiovascular diseases when the condition of the tyroid gland is euthyroid. In this case, the effect of the isotope causing a condition of moderate hypothyreosis probably amounts only to a lowering of the general metabolism to definite limits, to a diminution in the oxygen requirements of the tissues and hence to a diminution in the burden on the cardiovascular system. It should be added that, according to our data (A. F. Leshchinskiy and I. G. Dondua, A. F. Leshchinskiy, I. G. Dondua and V. V. Demidas),

radioactive iodine and radioactive phosphorus, both in experiments and in use in medical practice (thyreotoxicosis, polycytemia), result in a lowering of the percentage content of oxyhemoglobin, which apparently indicates a lowering of the oxidizing processes in the organism. Therapy with radioactive iodine should be combined with other necessary medical measures, since I^{131} does not affect the working of the heart directly.

The beginning of treatment and the repeated applications are preceded by a determination of the capacity of the thyroid gland to absorb radioactive iodine.

The method of treatment, according to Jaffe et al, consists in weekly internal administration of 6 microcuries of I^{131} in individual doses of 30mc. In the absence of improvement after a month, the treatments are repeated with the same doses. It is also possible to give a thrid treatment, if manifestations of hypothyroidism are absent. The authors point out that other clinics prescribe such high doses as 100 mc per treatment. The choice of a smaller dose is based on a diminution of the side effects of the preparation (thyroiditis, suppression of blood production, etc.) and is also due to the danger of temporary heightening of metabolism because of the entry of large amounts of thyroxine into the blood.

Blumgart et al propose that critically sick patients who cannot stand a temperary intensification of the function of the thyroid gland be given not more than 20 mc when in a euthyroid state (absorption 30% of I^{131}), and 10 mc when the absorption is higher and there are attacks of angina pectoris, these doses being repeated three times with interruptions of one week. Comparative investigations show that an instantaneous dose of 25 mc or one dose of 6 mc once a week for five weeks yield approximately the same type of result. There are indications that repeated small doses and a single dose of 100 mc produce the same results.

The use of radioactive iodine is regarded by Blumgart and co-authors as indicated only in those cases where the disease proceeds steadily for a long time (months or years). In their opinion, treatment with the isotope is contraindicated in cases of hypothyroidism, acute rheumatism, a fresh infarct of the myocardium, bronchoectasia, cirrhosis of the liver, and emotional instability. With rapidly progressing diseases (malignant hypertension, syphilitic aortitis), the application of radioactive iodine is not indicated. According to Wolferth et al, radioactive iodine is indicated for patients with a pronoumced syndrome of stenocardia accompanied by inability to work, in case the usual therapy is ineffective and when symptoms of hypothyreosis are absent. The authors think that there must not be a very high cholesterol content in the blood of these patients. It is recommended that the intake of fats be reduced; the patients should not smoke.

Summing up the results of the application of radioactive iodine to the severe form of stenocardia and cardiovascular failure in 50 clinics with 1,298 patients (including 87 observed by the authors), Blumgart et al point out that an improvement in their condition usually coincided with the appearance of hypothyreosis 2-6 months after the beginning of therapy. To avoid the development of myxedema, the patients received daily 6-12 mg of thyroid-gland extract. Out of 835 stenocardia patients (200 of them had cardiovascular failure), 78% showed a distinct improvement, while the condition of the rest was not improved perceptibly. Out of 463 sufferers from cardiovascular failure, 68% showed perceptible improvement, while the condition of the rest remained unchanged. The authors draw the conclusion that on the whole the treatment of patients with cardiovascular failure yields less satisfactory results than in the case of stenocardia, but more than 50% of the patients showed improvement, and 27% exhibited excellent results.

Jaffe et al observed 100 patients for four years or more, and 131 patients from six months to three years, with a number of the patients having had, before treatment, a combination of severe stenocardia and circulation failure, pronounced arrythmia and attacks of emphysema. The results of the radioactive iodine treatment are given in the table.

Effectiveness of Radioactive Iodine Therapy on Euthyroid Patients with Cardiovascular Diseases

Disease	Number of patients	Result of treatment in % of total number of patients			Source
		excellent	good	without improvement	
Stenocardia	658	40	36	24	Data from 47 clinics (quoted from Blumgart et al)
Heart failure	325	23	39	38	
Stenocardia	94	56	37	7	
Heart failure	78	53	28	19	Jaffe et al
Stenocardia and heart failure	59	48	32	20	
Stenocardia	62	39	32	29	Blumgart et al
Heart failure	25	16	36	48	

Along with this, there have been attempts at medical application of 113I to lung failure and intermittent lameness. The patients were subjected to the treatment only after trying the ordinarily used types of therapy and in cases where there was a sufficient

degree of absorption of the radioactive iodine by the thyroid gland.

The isotope was applied in doses similar to those used in the therapy of heart diseases, with the same indications and contraindications.

Discussing the results of the treatment of 13 patients with lung failure, Beiervaltes et al noted a rapid recovery of the ability to work in three of them. Hurst [Russian Garst] and Levine report improvement in eight out of twleve patients treated with radioactive iodine.

The proposal regarding the possibility of using radioactive iodine for intermittent lameness and other kinds of failure of the peripheral vessels is based on a few cases of relatively satisfactory effect from the application of I^{131}.

The data cited above attest the possibility of the medical application of radioactive iodine with definite success in certain cardiovascular diseases. This method deserves further study and improvement, especially with the object of lowering the applied doses of the isotope and working out other conditions for its rational utilization. Along with this, the raising of the sensitivity of the counting devices and the introduction of new radioactive-iodine preparations into practice will contribute to a wider diagonostic application of it.

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